General

Guideline Title

Obstetric cholestasis.

Bibliographic Source(s)

Royal College of Obstetricians and Gynaecologists (RCOG). Obstetric cholestasis. London (UK): Royal College of Obstetricians and Gynaecologists (RCOG); 2011 Apr. 14 p. (Green-top guideline; no. 43). [76 references]

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Royal College of Obstetricians and Gynaecologists (RCOG). Obstetric cholestasis. London (UK): Royal College of Obstetricians and Gynaecologists (RCOG); 2006 Jan. 10 p. (Guideline; no. 43).

Recommendations

Major Recommendations

In addition to these evidence-based recommendations, the guideline development group also identifies points of best clinical practice in the original guideline document.

Classification of evidence levels (1++ to 4) and grades of recommendations (A-D) are defined at the end of the "Major Recommendations" field.

How Is Obstetric Cholestasis Diagnosed?

C - Pregnancy-specific reference ranges for liver function tests (LFTs) should be used.

C - Other causes of itching and of liver dysfunction should be excluded.

C - Women with persistent pruritus and normal biochemistry should have LFTs repeated every 1–2 weeks.

C - Postnatal resolution of pruritus and LFTs should be confirmed.

Other causes of pruritus must be excluded. The skin should be inspected and care must be taken to differentiate dermatographia artefacta (skin trauma from intense scratching),which may be seen in obstetric cholestasis, from other common skin conditions such as eczema or atopic eruption of pregnancy (previously referred to as eczema of pregnancy, prurigo and pruritic folliculitis). If a rash is present, polymorphic eruption of pregnancy or pemphigoid gestations (blisters) should be considered.

Other evidence of cholestasis should be sought, including pale stool, dark urine and jaundice, and other risk factors identified such as a personal or family history of obstetric cholestasis, multiple pregnancy, carriage of hepatitis C and presence of gallstones.

In clinical practice, otherwise unexplained abnormalities in transaminases, gamma-glutamyl transferase and/or bile salts are considered sufficient to support the diagnosis of obstetric cholestasis. The increase in alkaline phosphatase in pregnancy is usually placental in origin and so does not normally reflect liver disease. A thorough history and examination should be carried out, including a drug history, before abnormal LFTs are determined to be otherwise unexplained. Bilirubin is raised only infrequently and most women will have increased levels of one or more of the remaining LFTs. Although a wide variety of cutoff points have been used for defining abnormality in LFTs and bile salts, the upper limit of pregnancy-specific ranges should be applied. For transaminases, gamma-glutamyl transferase and bilirubin, the upper limit of normal throughout pregnancy is 20% lower than the non-pregnant range. Many laboratories will use pregnancy-specific ranges for bile salts, but this should not be assumed. Bile acid levels can rise significantly after a meal, so while fasting might give lower values and help the diagnosis to be avoided in a few women with otherwise normal LFT, in the majority of studies and in clinical practice random levels are generally used. Some women will have pruritus for days or weeks before the development of abnormal liver function: in those with persistent unexplained pruritus and normal biochemistry, LFTs should be measured every 1–2 weeks. Isolated elevation of bile salts may occur but this is uncommon; normal levels of bile salts do not exclude the diagnosis.

Other causes of pruritus and abnormal LFTs should be sought. This may include carrying out a viral screen for hepatitis A, B, and C, Epstein Barr and cytomegalovirus, a liver autoimmune screen for chronic active hepatitis and primary biliary cirrhosis (for example, anti-smooth muscle and antimitochondrial antibodies) and liver ultrasound. Pre-eclampsia and acute fatty liver of pregnancy are pregnancy-specific causes of abnormal LFTs that might form part of the differential diagnosis in atypical or early cases.

How Should Obstetric Cholestasis Be Monitored?

D - Postnatally, LFTs should be deferred for at least 10 days.

Typically, transaminases will range from just above the upper limit of normal to several hundreds. Regular LFTs, along with a general review, blood pressure measurement and urine check, allow monitoring of the condition and exclusion of other diagnoses. If LFTs return to normal, obstetric cholestasis is not likely to be the correct diagnosis. If LFTs escalate very rapidly, additional diagnoses need to be considered and the frequency of monitoring increased: although this situation can be consistent with obstetric cholestasis, it is not typical. A coagulation screen should be performed.

What Is the Risk of Stillbirth for Pregnancies Complicated by Obstetric Cholestasis?

B - In a hospital setting, the current additional risk of stillbirth in obstetric cholestasis above that of the general population has not been determined but is likely to be small.

What Additional Risks Are Associated with Pregnancies Complicated by Obstetric Cholestasis?

B - Obstetricians should be aware (and should advise women) that the incidence of premature birth, especially iatrogenic, is increased.

B - Women should be advised of the increased likelihood of meconium passage in pregnancies affected by obstetric cholestasis.

B - Women with obstetric cholestasis should be booked in under consultant-led, team-based care and give birth in a hospital unit.

Can Fetal Death Be Predicted and Prevented?

B - Poor outcome cannot currently be predicted by biochemical results and delivery decisions should not be based on results alone.

D - No specific method of antenatal fetal monitoring for the prediction of fetal death can be recommended.

C - Ultrasound and cardiotocography are not reliable methods for preventing fetal death in obstetric cholestasis.

Should Women with Obstetric Cholestasis Be Offered Elective Early Delivery?

B - Women should be informed of the increased risk of perinatal morbidity from early intervention (after 37^{+0} weeks of gestation).

B - Women should be informed of the increased risk of maternal morbidity from intervention at 37^{+0} weeks of gestation.

Stillbirths in obstetric cholestasis have been reported across all gestations. As gestation advances, the risk of delivery (prematurity, respiratory distress, failed induction) versus the uncertain fetal risk of continuing the pregnancy (stillbirth) may justify offering women induction of labour after 37^{+0} weeks of pregnancy. The decision should be made after careful counselling. The case for intervention at this gestation may be stronger in those with more severe biochemical abnormality.

What Treatment, if Any, Should Be Used to Treat Obstetric Cholestasis and What Benefit Can Be Expected?

There is no evidence that any specific treatment improves fetal or neonatal outcomes. All such therapies should be discussed with the individual woman with this in mind.

Topical Emollients

C - Topical emollients are safe but their efficacy is unknown.

S-Adenosyl Methionine

A - There is insufficient evidence to demonstrate whether S-adenosyl methionine (SAMe) is effective for either control of maternal symptoms or for improving fetal outcome, and it is not recommended.

Ursodeoxycholic Acid (UDCA)

A - UDCA improves pruritus and liver function in women with obstetric cholestasis.

Dexamethasone

D - Dexamethasone should not be first-line therapy for treatment of obstetric cholestasis, nor should it be used outside of a randomised controlled trial (RCT) without a thorough consultation with the woman.

What is the Role of Vitamin K?

D - Women should be advised that when prothrombin time is normal, water-soluble vitamin K (menadiol sodium phosphate) in low doses should be used only after careful counselling about the likely benefits but small theoretical risk.

What Follow-up Should Be Offered to Women Who Have Had a Pregnancy Affected by Obstetric Cholestasis?

As a minimum, healthcare practitioners must ensure that LFTs return to normal, pruritus resolves, all investigations carried out during the pregnancy have been reviewed and the mother has fully understood the implications of obstetric cholestasis. The latter will include reassurance about the lack of long-term sequelae for mother and baby and discussion of the high recurrence rate (45%–90%), contraceptive choices (usually avoiding estrogen-containing methods) and the increased incidence of obstetric cholestasis in family members. Local policy will dictate how this is best organised, but LFTs at 6 weeks after delivery and an appointment at 8 weeks is a suggested model. Appropriate follow-up should be arranged by a medical practitioner with appropriate skills.

Definitions:

Grades of Recommendations

A - At least one meta-analysis, systematic review or randomised controlled trial rated as 1++, and directly applicable to the target population; *or*

A systematic review of randomised controlled trials or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating overall consistency of results

B - A body of evidence including studies rated as 2++ directly applicable to the target population, and demonstrating overall consistency of results; *or*

Extrapolated evidence from studies rated as 1++ or 1+

C - A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results; *or*

Extrapolated evidence from studies rated as 2++

D - Evidence level 3 or 4; *or*

Extrapolated evidence from studies rated as 2+

Good Practice Point - Recommended best practice based on the clinical experience of the guideline development group

Classification of Evidence Levels

1++ High-quality meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a very low risk of bias

1+ Well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias

1– Meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a high risk of bias

2++ High-quality systematic reviews of case–control or cohort studies or high-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal

2+ Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal

2– Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal

3 Non-analytical studies, e.g., case reports, case series

4 Expert opinion

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Obstetric cholestasis (also referred to as intrahepatic cholestasis of pregnancy)

Guideline Category

Diagnosis

Evaluation

Management

Treatment

Clinical Specialty

Family Practice

Internal Medicine

Obstetrics and Gynecology

Intended Users

Physician Assistants

Physicians

Guideline Objective(s)

- To summarise the evidence for the fetal risks associated with obstetric cholestasis
- To provide guidance on the different management choices and the options available for its treatment

Target Population

Women with diagnosed or suspected obstetric cholestasis

Interventions and Practices Considered

Assessment/Diagnosis

1. Liver function tests
    - Transaminases
    - Gamma-glutamyl transferase
    - Bilirubin and/or bile salts
2. Personal and family history and physical examination
3. Screening for hepatitis A, B, and C virus; Epstein Barr virus; cytomegalovirus; chronic active hepatitis; primary biliary cirrhosis; pre-eclampsia; acute fatty liver; presence of gallstones
4. Liver ultrasound
5. Risk assessment for and advising women concerning fetal and maternal complications

Management/Treatment

1. Consultant-led, team-based care
2. Counselling on early elective delivery
3. Ursodeoxycholic acid
4. Dexamethasone (not as first-line therapy and only with consultation or in a randomised controlled trial)
5. Vitamin K supplements (only after counselling)
6. Post-natal confirmation of diagnosis

Note: The following are considered but not recommended: fetal monitoring for the prediction of fetal death, fetal ultrasound or cardiotocography for preventing fetal death, topical emollients, S-adenosyl methionine (SAMe).

Major Outcomes Considered

- Maternal morbidity and mortality
- Fetal risks (including prematurity and intrauterine death)

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

This guideline was developed in accordance with standard methodology for producing RCOG Green-top guidelines (see the "Availability of Companion Documents" field). Medline, EMBASE, the Cochrane library including the Cochrane Database of Systematic Reviews, the Cochrane Control Register of Controlled Trials (CENTRAL), the Database of Abstracts of Reviews and Effects (DARE), the ACP Journal Club and Ovid database, including in-process and other non-indexed citations, were searched using the relevant Medical Subject Heading (MeSH) terms, including all subheadings, between 2003 and January 2010. This was combined with a keyword search. Search words included 'cholestasis',

'intrahepatic cholestasis', 'ursodeoxycholic acid', 's-adenosylmethionine', 'vitamin K', 'bile pigments', 'pruritus', 'bilirubin', 'transaminases', 'pregnancy complications', 'dexamethasone', 'congenital' and 'neonatal diseases and abnormalities', 'embryo and fetal development', 'developmental disabilities', 'newborn disease', 'prenatal disorder', 'nervous system disorder', 'liver function tests', 'bile acids and salt' and 'aminotransferase'. The search was limited to humans and the English language. Selection of articles for analysis and review was then made based on relevance to the objectives.

The National Library for Health and the National Guideline Clearinghouse were also searched for relevant guidelines and reviews. Only one other guideline was identified.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Classification of Evidence Levels

1++ High-quality meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a very low risk of bias

1+ Well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias

1– Meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a high risk of bias

2++ High-quality systematic reviews of case–control or cohort studies or high-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal

2+ Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal

2– Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal

3 Non-analytical studies, e.g., case reports, case series

4 Expert opinion

Methods Used to Analyze the Evidence

Systematic Review

Description of the Methods Used to Analyze the Evidence

Reviewing and Grading of Evidence

Once the evidence has been collated for each clinical question it needs to be appraised and reviewed (refer to section 3 in "Development of RCOG Green-top guidelines: producing a clinical practice guideline" for information on the formulation of the clinical questions; see the "Availability of Companion Documents" field). For each question, the study type with least chance of bias should be used. If available, randomised controlled trials (RCTs) of suitable size and quality should be used in preference to observational data. This may vary depending on the outcome being examined.

The level of evidence and the grade of the recommendations used in this guideline originate from the guidance by the Scottish Intercollegiate Guidelines Network (SIGN) Grading Review Group, which incorporates formal assessment of the methodological quality, quantity, consistency,

and applicability of the evidence base. The methods used to appraise individual study types are available from the SIGN Web site (www.sign.ac.uk/methodology/checklists.html). An objective appraisal of study quality is essential, but paired reviewing by guideline leads may be impractical because of resource constraints.

Once evidence has been collated and appraised, it can be graded. A judgement on the quality of the evidence will be necessary using the grading system (see the "Rating Scheme for the Strength of the Evidence" field). Where evidence is felt to warrant 'down-grading', for whatever reason, the rationale must be stated. Evidence judged to be of poor quality can be excluded. Any study with a high chance of bias (either 1– or 2–) will be excluded from the guideline and recommendations will not be based on this evidence. This prevents recommendations being based on poor-quality RCTs when higher-quality observational evidence is available.

Methods Used to Formulate the Recommendations

Expert Consensus

Informal Consensus

Description of Methods Used to Formulate the Recommendations

Guideline Development

The development of guidelines involves more than the collation and reviewing of evidence. Even with high-quality data from systematic reviews of randomised controlled trials, a value judgement is needed when comparing one therapy with another. This will therefore introduce the need for consensus.

Royal College of Obstetricians and Gynaecologists (RCOG) Green-top guidelines are drafted by nominated developers, in contrast to other guideline groups such as the National Institute for Health and Clinical Excellence (NICE) and the Scottish Intercollegiate Guidelines Network (SIGN), who use larger guideline development groups. Equally, in contrast to other guideline groups, the topics chosen for development as Green-top guidelines are concise enough to allow development by a smaller group of individuals.

In agreeing the precise wording of evidence-based guideline recommendations and in developing consensus-based 'good practice points', the Guidelines Committee (GC) will employ an informal consensus approach through group discussion. In line with current methodologies, the entire development process will follow strict guidance and be both transparent and robust. The RCOG acknowledges that formal consensus methods have been described, but these require further evaluation in the context of clinical guideline development. It is envisaged that this will not detract from the rigor of the process but prevent undue delays in development.

Rating Scheme for the Strength of the Recommendations

Grades of Recommendations

A - At least one meta-analysis, systematic review or randomised controlled trial rated as 1++, and directly applicable to the target population; *or*

A systematic review of randomised controlled trials or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating overall consistency of results

B - A body of evidence including studies rated as 2++ directly applicable to the target population, and demonstrating overall consistency of results; *or*

Extrapolated evidence from studies rated as 1++ or 1+

C - A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results; *or*

Extrapolated evidence from studies rated as 2++

D - Evidence level 3 or 4; *or*

Extrapolated evidence from studies rated as 2+

Good Practice Point - Recommended best practice based on the clinical experience of the guideline development group

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

Following discussion in the Guidelines Committee (GC), each Green-top guideline is formally peer reviewed. At the same time, the draft guideline is published on the Royal College of Obstetricians and Gynaecologists (RCOG) Web site for further peer discussion before final publication.

All comments will be collated by the RCOG and tabulated for consideration by the guideline leads. Each comment will require discussion. Where comments are rejected then justification will need to be made. Following this review, the document will be updated and the GC will then review the revised draft and the table of comments.

Once the GC signs-off on the guideline, it is submitted to the Standards Board for approval before final publication.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for most recommendations (see the "Major Recommendations" field).

Where possible, recommendations are based on available evidence. The areas where evidence is lacking are annotated as 'good practice points' in the original guideline document.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate diagnosis and management of obstetric cholestasis to improve maternal and fetal outcomes

Potential Harms

There is an increased risk of perinatal morbidity from early intervention (after 37^{+0} weeks of gestation).

Qualifying Statements

Qualifying Statements

The Royal College of Obstetricians and Gynaecologists (RCOG) produces guidelines as an educational aid to good clinical practice. They present recognised methods and techniques of clinical practice, based on published evidence, for consideration by obstetricians and gynaecologists and

other relevant health professionals. The ultimate judgement regarding a particular clinical procedure or treatment plan must be made by the doctor or other attendant in the light of clinical data presented by the patient and the diagnostic and treatment options available. This means that RCOG guidelines are unlike protocols or guidelines issued by employers, as they are not intended to be prescriptive directions defining a single course of management. Departure from the local prescriptive protocols or guidelines should be fully documented in the patient's case notes at the time the relevant decision is taken.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Audit Criteria/Indicators

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

Royal College of Obstetricians and Gynaecologists (RCOG). Obstetric cholestasis. London (UK): Royal College of Obstetricians and Gynaecologists (RCOG); 2011 Apr. 14 p. (Green-top guideline; no. 43). [76 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2006 Jan (revised 2011 Apr)

Guideline Developer(s)

Royal College of Obstetricians and Gynaecologists - Medical Specialty Society

Source(s) of Funding

Royal College of Obstetricians and Gynaecologists

Guideline Committee

Guidelines Committee

Composition of Group That Authored the Guideline

Authors: Dr AP Kenyon MRCOG, London; Ms JC Girling FRCOG, Middlesex

Peer Reviewers: British Maternal and Fetal Medicine Society; British Liver Trust; Foundation for Liver Research; OC Support UK; RCOG Consumers' Forum; RCPCH; Dr JE Brennand FRCOG, Glasgow; Mr AJ Kelly MRCOG, Brighton; Professor C Nelson-Piercy FRCOG, London; Dr MM Ramsay FRCOG, Nottingham; Dr AJ Thomson MRCOG, Paisley, Scotland; Professor JG Thornton FRCOG, Nottingham; Mr SA Walkinshaw FRCOG, Liverpool; Professor C Williamson, Professor of Obstetric Medicine, London

Committee Lead Peer Reviewers: Mr Griffiths FRCOG, Luton; Dr Siddiqui FRCOG, Glasgow, Scotland

Financial Disclosures/Conflicts of Interest

None declared

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Royal College of Obstetricians and Gynaecologists (RCOG). Obstetric cholestasis. London (UK): Royal College of Obstetricians and Gynaecologists (RCOG); 2006 Jan. 10 p. (Guideline; no. 43).

Guideline Availability

Electronic copies: Available from the Royal College of Obstetricians and Gynaecologists (RCOG) Web site .

Availability of Companion Documents

The following are available:

- Development of RCOG Green-top guidelines: policies and processes. Clinical Governance Advice No 1a. London (UK): Royal College of Obstetricians and Gynaecologists (RCOG); 2006 Nov. 6 p. Electronic copies: Available from the Royal College of Obstetricians and Gynaecologists (RCOG) Web site .
- Development of RCOG Green-top guidelines: producing a scope. Clinical Governance Advice No 1b. London (UK): Royal College of Obstetricians and Gynaecologists (RCOG); 2006 Nov. 4 p. Electronic copies: Available from the RCOG Web site .
- Development of RCOG Green-top guidelines: producing a clinical practice guideline. Clinical Governance Advice No 1c. London (UK): Royal College of Obstetricians and Gynaecologists (RCOG); 2006 Nov. 13 p. Electronic copies: Available from the RCOG Web site .

- Development of RCOG Green-top guidelines: consensus methods for adaptation of Green-top guidelines. Clinical Governance Advice No 1d. London (UK): Royal College of Obstetricians and Gynaecologists (RCOG); 2010 Feb. 9 p. Electronic copies: Available from the RCOG Web site .

In addition, suggested audit topics can be found in section 14 of the original guideline document .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI on March 10, 2006. The information was verified by the guideline developer on April 26, 2006. This NGC summary was updated by ECRI Institute on January 26, 2012.

Copyright Statement

Disclaimer

NGC Disclaimer